Probing retinal function with a multi-layered simulator

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Introduction

Our brain can recreate images from interpreting a stream of information emitted by ~1 million parallel channels in the retina. This ability is partly due to the astonishing functional and anatomical diversity of the retinal ganglion cells (RGCs), each interpreting a different feature of the visual scene. In addition, RGCs talk to each other during complex tasks (especially motion handling), via amacrine cells (ACs - lateral connectivity) or gap junctions.

To better understand the respective role of specific cells type in vision:
Switch them ON or OFF.

We modify pharmacologically the excitability of specific cell populations using pharmacogenetics (DREADDs technology).

We propose a computational model of specific RGCs and ACs activity, that express DREADDs.

We simulate this model using a novel simulation platform that can reflect **normal** and **impaired** retinal function from **single-cell** to **large-scale** level.

We explore the effects on the **individual** and **collective** response to different stimuli.

Experiments

Pharmacogenetics: Control neuronal activity **in-vivo, non-invasively, reversibly and fast** by using the **Designer Receptors Exclusively Activated by Designer Drugs** (DREADDs) technique. DREADD-expressing cells' activity can be **increased** or **reduced** when the synthetic designer drug clozapine N-oxide (CNO) is added to the solution[1].

What is the impact on vision?

RGCs and/or ACs can express DREADDs.

The effect is not clear on experimental grounds, since these cell types "antagonize" each other.

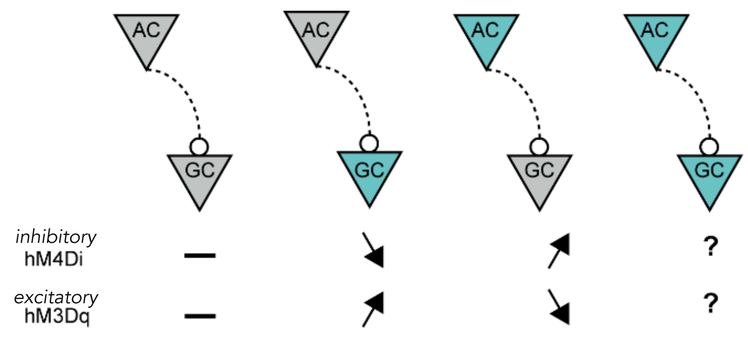


FIGURE 1. DREADDs in ACs makes the interpretation of functional results from DREADD-expressing RGCs more challenging.

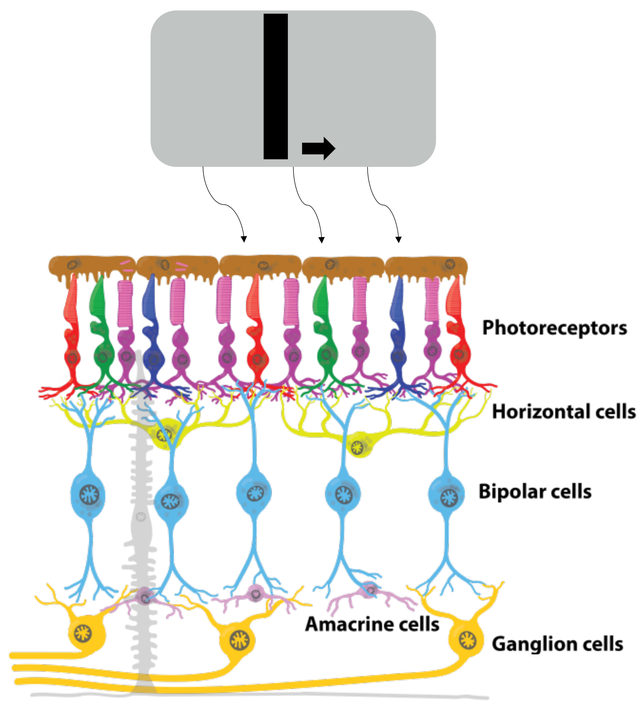
Courtesy of Gerrit Hilgen

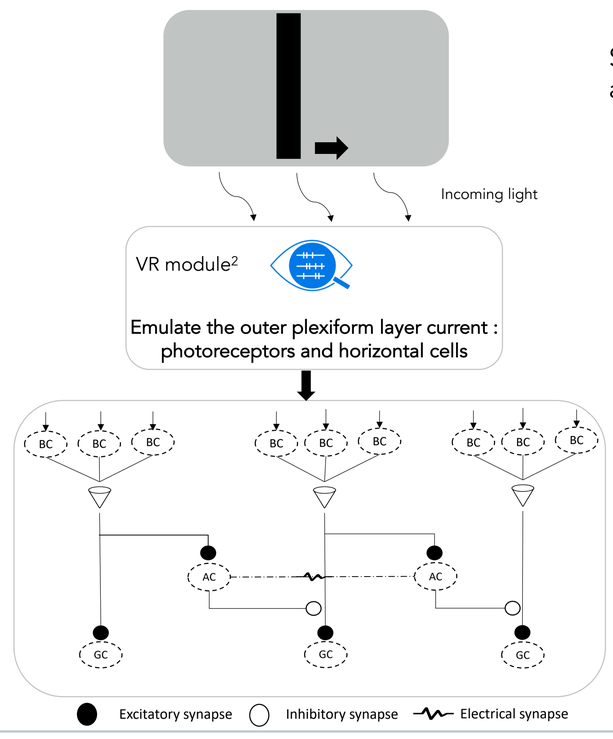
Disclaimer: All the experimental work is done at Prof. Sernagor's lab

Retina model

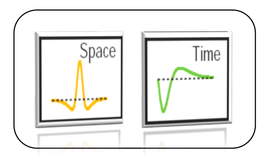
Retinal processing

The retina has both a **feed-forward** structure, from photoreceptors to bipolar cells and onwards to RGCs and a **lateral** structure, due to inhibitory interneurons comprising two groups; horizontal and amacrine cells. These neurons are organized into multiple functional circuits that operate in parallel and converge onto RGCs, thus allowing them to efficiently process visual information at a **single** and **population** level.
Local (single level) information can be read in the spikes emitted by a single RGC (firing rate, latency of the first spike) and non-local (population level) information is provided by the lateral connections from horizontal and amacrine cells that induce indirect interactions between RGCs.

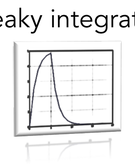




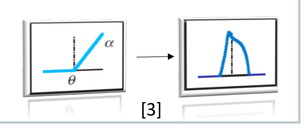
Stimulus convolution with a spatio-temporal kernel



Leaky integrator



Linear-Nonlinear cascade



[3]

Retina simulator

Macular

Work in progress

Our novel numerical platform, called **Macular,** is designed to simulate and test hypotheses in normal and impaired retinal conditions from single-cell to large-scale level. It is able to handle different visual processing circuits and allows us to visualize responses to visual scenes (movies). Macular also allows us to mimic specific pathologies or pharmacologically induced impairments that can be controlled by tunable parameters, as well as to emulate electric stimulation by prostheses.

Disclaimer: Macular is under development, in collaboration with the DREAM-SED service of INRIA SAM.

Simulations

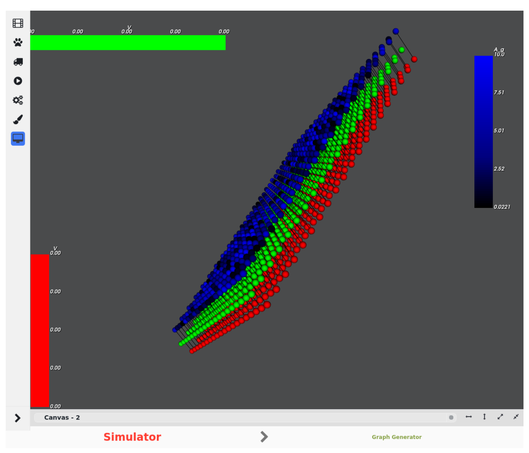
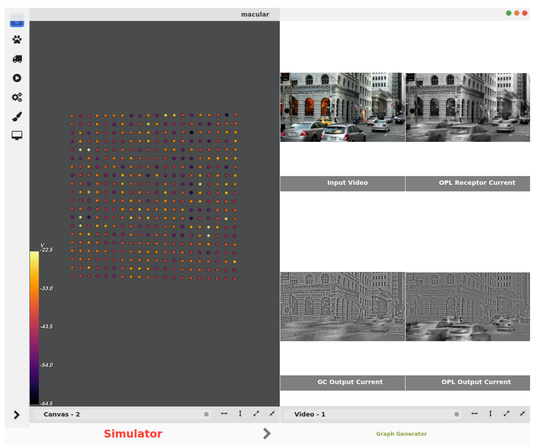


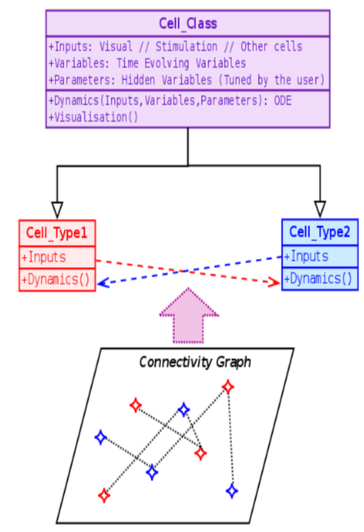
Figure 3. The retinal response to a movie at different layers of the retina. **Left tab:** RGC layer **Right tab:** Four panels including the stimulus and the response to it at earlier stages of retinal processing.

Figure 2. **3D visualization of retinal layers.** The user can view each neuronal layer of the retina and the interactions among the same or different layers in 3D. Implementation of V1 cortical activation is under development.



Macular's structure

A cell is not necessarily a biological cell, it can be a group of cells.



Summary

Switching ON or OFF RGCs and/or ACs may impact the RGCs **individual** response but also their **concerted** activity to different stimuli, thus allowing us to understand how they contribute to the encoding of complex visual scenes. However, it is difficult to distinguish on pure experimental grounds the effect of CNO when both cell types express DREADDs, as these cells "antagonize" each other. Contrarily, numerical simulation can afford it.

✓ We propose a computational model of the CNO effect.
✓ We develop a novel numerical platform to simulate and test this effect.

Perspectives:
- Tune the simulator to reproduce experimental results.
- Study the CNO effect on the single-cell and population level.
- Anticipate new experiments.

References

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